Dimethyl Sulfoxide (DMSO) Health and Safety Information

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Introduction

This bulletin summarizes the available industrial hygiene and toxicological data for Dimethyl Sulfoxide (DMSO). DMSO is an unusually nontoxic organic solvent that is finding increased use in pharmaceutical synthesis, the manufacture of electronics, and drug delivery in the body. Its use is supported by over 45 years of industrial and academic experience.

Contents:

Gaylord Chemical Company, L.L.C. (GCC) is the world's leading provider of Dimethyl Sulfoxide (DMSO) solutions. Beginning in the early 1960's ,GCC has been dedicated to the development of new uses for DMSO. In order to meet customer-specific needs, GCC has pioneered the development of multiple grades of DMSO, including DMSO USP.

Gaylord Chemical's solutions-based approach has contributed to the development and growth of industries including pharmaceuticals, hydrocarbons, electronics, polymers, coatings, agricultural chemicals, and industrial cleaners.

Gaylord Chemical's headquarters are located in Slidell, Louisiana with manufacturing, research, and development facilities in nearby Bogalusa, Louisiana. GCC remains the only producer of DMSO in the Western Hemisphere.

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Overview

A great number of toxicological, environmental and medical studies have been performed with DMSO to determine the safety of this chemical. Many of these studies have been published as references at the end of this bulletin. This summary only lists some of the results found, but in-depth details are reported in the original publications. A substantial dossier of data was submitted to the EPA for the HPV "High Production Volume" program by a consortium of producers including Gaylord Chemical. This data is available on the EPA website at http://www.epa.gov/chemrtk/pubs/summaries/dimthslf/c14721tc.htm. In addition, Gaylord Chemical's extensive database of over 23,000 articles on applications and safe process use with DMSO is available for use by those who request it.

DMSO is a commercially manufactured dipolar aprotic solvent which is also a naturally occurring substance. It is apparently a part of earth's complex sulfur cycle. DMSO is created in the atmosphere at a rate of 20-60 billion pounds per year from dimethyl sulfide, which is produced by metabolic processes in soil and sediments. DMSO is also found in natural waters and soil. Metabolism of DMSO in soil by microorganisms results in the formation of sulfur and dimethyl sulfide. DMSO is also reported to be present at low concentrations (<0.05-3.7 ppm) in food products such as sauerkraut, tomato paste, milk, beer, coffee, tea and in forage crops such as alfalfa and corn silage.

DMSO has low acute and chronic toxicity for animal, plant and aquatic life. Exposure to test organisms at high concentrations by contact, ingestion or inhalation consistently show low toxicity. DMSO is not listed as a carcinogen by regulatory authorities and is actually used as a neutral solvent in the Ames mutagenicity tests. DMSO is not a teratogen in mice, rats or rabbits. Because of this low potential for toxicity, the EPA has approved DMSO as a solvent or a cosolvent, in pesticides which are applied before crop emergence or prior to the formation of edible parts of food plants.

In 1978, the FDA approved the use of DMSO in a 50/50 mixture with water as an effective treatment for the symptoms of interstitial cystitis. Since then, a large number of people have received this treatment. The product is marketed today by Edwards Life Sciences under the trade name of Rimso-50™. DMSO has been approved for use in other pharmaceutical formulations in the U.S. and other countries. In addition, in 1998, the FDA endorsed the recommendation of the expert working group of the International Conference on Harmonization relative to the residual solvents in pharmaceuticals. DMSO was placed in the safest category, class 3 solvents, with low toxic potential. Class 3 includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals. Solvents in Class 3 (Table 1) may be regarded as less toxic and of lower risk to human health. Available data indicate that they are less toxic in acute or short-term studies and negative in genotoxicity studies. It is considered that amounts of these residual solvents of 50 mg per day or less (corresponding to 5,000 ppm or 0.5 percent under Option 1) would be acceptable without justification. Higher amounts may also be acceptable provided they are realistic in relation to manufacturing capability and good manufacturing practice (GMP).

When handling or using DMSO, a potential for exposure exists. Therefore, the following information should be considered regarding possible exposure routes. Skin contact, the most likely exposure, has been extensively studied with humans and animals. Large dosages over prolonged periods showed only minor toxic effects such as minor skin irritation, itching and burning Although DMSO is absorbed rapidly through the skin, it has a low degree of toxicity *via* dermal route of administration. Also, it has been found that the molecular weight of chemical compounds can preclude their transdermal penetration by DMSO. For instance, DMSO enhances the penetration of butyl acetate in solution, while octyl acetate is a “nonpermeator”.[15]

DMSO is not alone in its ability to penetrate human skin, and proper industrial hygiene should be practiced when working with all solvents. Table 2 provides relative permeability data for some common solvents.

Table 1 Class 3 Solvents International Conference on Harmonization Endorsed by the FDA*	
Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl acetate	Methylethyl ketone
tert-Butylmethyl ether	Methylisobutyl ketone
Cumene	2-Methyl-1-propanol
Dimethyl sulfoxide	Pentane
Ethanol	1-Pentanol
Ethyl acetate	1-Propanol
Ethyl ether	2-Propanol
Ethyl formate	Propyl acetate
Formic acid	
***Should Be Limited by GMP or Other Quality-Based Requirements**	

Figure 2. Permeability Constants of Commercial Solvents	
	(g/m^2h)
Dimethyl Sulfoxide	176 ± 42
N-methyl pyrrolidone (NMP)	171 ± 59
Dimethyl acetamide	107 ± 19
Dimethyl formamide (DMF)	98 ± 1.1

Physical Properties of DMSO

Some of the physical properties of DMSO are included in the following table. For a more extensive list, please refer to Gaylord's Bulletin 101, "Dimethyl Sulfoxide (DMSO) Physical Properties."

Physical Property	Metric Units	English Units
Freezing Point	18.55°C	65.4°F
Boiling Point - 760 mm	189°C	372 ° F
Vapor Pressure - 0.6 in Hg	25 °C	77°F
- 13 in Hg	100 ° C	212 ° F
- 310 in Hg	150°C	302 ° F
Heat of Vaporization @ 70°C	11.3 Kcal/mol	260 BTU/lb.
Flash Point (open cup)	95°C	203° F
Flash Point (closed cup)	89°C	192°F
Auto-ignition Temperature in Air	300-302 ° C	572-575 ° F
Flammability Limits in Air - Lower (100°C) Upper	3-3.5% by volume 42-63%	
Solubility Parameter, Total	13 $(cal/cm^3)^{1/2}$	

Solubility

A large amount of solubility data has been compiled. Please refer to Gaylord's Bulletin 102, "Dimethyl Sulfoxide (DMSO) Solubility Data" for information on solubility of organic, inorganic, and pharmaceutical compounds.

Reactivity

DMSO reacts very rapidly and vigorously with a number of materials, particularly with those that also react rapidly with water. The reactions are highly exothermic, with rapid steam or gas evolution. In most cases these reactions can be controlled by rate or order of addition or by arranging adequate heat removal. The following types of compounds require care to prevent extremely rapid reactions.

1. Strong oxidizing agents such as perchlorates, permanganates, iodine pentafluoride, silver fluoride and others react very rapidly.
2. Acid chlorides react with DMSO at about the same rate as with ethyl alcohol.
3. Carboxylic acid anhydrides react rapidly.
4. Alkali hydrides used for making DMSO anion require adequate heat removal. (A technical bulletin on reactions of the dimsyl anion is available.)

5. DMSO cannot be used with Ziegler-Natta catalysts or in Friedel-Crafts reactions.
6. Methyl bromide can react to form HBr and Br_2. Uncontrolled reactions have resulted.

Additional information is available from Gaylord Chemical Company.

Acute Toxicity

Evaluation of the degree of hazard due to contact with a chemical is usually by its single-dose LD-50. The LD-50 is the Lethal Dose in number of grams of DMSO per kilogram of body weight which results in 50% mortality of the test animals under standardized conditions. Dozens of test data reports are available from many laboratories throughout the world. The reported LD-50 may vary but the data confirm a low level of toxicity. One published summary is the following

	Single-Dose Toxicity of DMSO as LD-50[(1)] (g/kg)				
Species	Mode of Treatment				
	Applied to Skin	Taken by Mouth	Into Blood Stream	Beneath Skin	Into Body Cavity
Mouse	50	16.5-24.6	3.8-8.9	13.9-20.5	14.7-17.0
Rat	40	17.4-28.3	5.2-8.1	12.0-20.5	13.0
Guinea Pig	-	11.0	-	-	5.5
Chicken	-	14.0	-	-	-
Cat	-	-	4.0	-	-
Dog	>11	10.0	2.5	-	-
Monkey	>11	4.0	4.0	-	-

Using the monkey as an example, it would take more than 1.6 pounds applied to the skin or 0.6 pounds taken by mouth or injected directly into the blood stream, to have a 50% mortality rate in a group weighing 150 pounds each.

Other studies have shown that DMSO has low acute toxicity and is practically non-toxic (LD-50>5 g/kg) by ingestion or dermal application. Rat oral LD-50s are reported from 17.4 to 28.3 g/kg, whereas LD-50s for mice have been reported from 16.5 to 24.6 g/kg. The acute dermal LD-50 is 40 g/kg for the rat and 50 g/kg for the mouse, while dermal LD-50s > 11 g/kg are reported for both dogs (beagles) and primates (rhesus monkeys). Although DMSO can cause skin and eye irritation, it is not a skin sensitizer.

In addition to LD-50 explained above, another unit LC-50 is used to evaluate the hazard from inhalation. LC-50 is the Lethal Concentration that kills 50% of the test animals. The acute rat inhalation LC-50 is greater than 1.6 mg /l, the only dose level tested, and which is also a No-Observed-Effect-Level (NOEL).[(10)]

Subchronic Toxicity

The subchronic rat inhalation NOEL of 200 mg/m^3 (0.2 mg/l) was determined from a single concentration study. Extensive monitoring of human patients have shown that DMSO does not affect human renal function. DMSO is a diuretic but no sign of kidney damage has been found in humans or laboratory animals after repeated DMSO treatment. Hemolysis has been reported in animals that received DMSO intravenously.

Skin Exposure

DMSO easily penetrates the skin (176 ± 42 g/m^2/hr) compared to, for example, water (14.8 ± 0.1 g/m^2/hr), but because of DMSO's low toxicity (see previous section) and the fact that this same permeability test showed DMSO does not carry less-permeable substances with it through the skin, it can be concluded that DMSO does not pose a significant threat by skin absorption. The penetration rate of DMSO in solutions is a direct function of the mole fraction of DMSO. (Ursin, et. al. 1995)[14]. Although DMSO readily penetrates human skin in concentrations of 70-100%, at concentrations of 67% or less, DMSO molecules are hydrated, which greatly reduces dermal penetration (Sulzberger et. al., 1966; Brayton, 1986: Woodford and Barry, 1986).

No significant abnormalities were found in extensive physical examinations or analyses of blood and urine during repeated applications of large amounts of DMSO to the skin of humans over a long period of time. This was reported by Dr. Richard Brobyn [(2)] to the New York Academy of Sciences. DMSO was used in two human studies lasting 14 and 90 days. In each case, one gram of DMSO per kilogram of body weight was applied each day by each subject to his own skin. In an (80 kg = 176 lb) individual, it was 80 grams or 2.7 fl. oz. This amount required up to 2 hours for complete absorption from the 90% DMSO gel.

No frank evidence of intolerance resulted from dermal application of 9 grams/kilogram of 90% DMSO to Rhesus monkeys daily for 18 months. In a small (50 kg = 110 lb.) individual, this would amount to daily applications of 15.2 fluid ounces or nearly a pint of 90% DMSO.

Observation has indicated that skin application, particularly if frequent with large amounts of DMSO, may result in reddening, itching and burning at the application site. Exposure to large amounts of DMSO by skin or elsewhere may result in sedation, headache, nausea or dizziness.

Chronic Toxicity

DMSO is not listed as a carcinogen by regulatory agencies such as IARC, NTP, OSHA or ACGIH, based on reviews of numerous studies. An 18-month study with rhesus monkeys established an oral NOEL of 3300 mg/kg/day. No tumors were observed and bone marrow smears from the monkeys that received oral or topical doses of DMSO at up to 9 g/kg/day.[12] This is comparable to an average human (70 kg or 154 lbs) consuming approximately 210 g (or nearly 1/2 pound) DMSO per day, i.e., 3g/kg/day. In fact, 84 humans that have received daily topical treatment of 2.8 g DMSO/kg/day (equivalent to nearly 1/2 pound/day/person) for up to three months showed no DMSO-related effects beyond occasional skin irritation, garlicky breath and body odor. Additionally, (Hull et al. 1969)[(7)] found no DMSO-related effects in any of the 38 humans, age 21-55, who received a topical application of an 80% DMSO gel in a single daily dose of 1 g/kg for 12 weeks.

Continuing research has demonstrated that the ocular effects reported from DMSO treatment of dogs, rabbits, guinea pigs and swine are species-specific and not reproducible in primates, including humans. Even though ocular toxicity, specifically lenticular refractive changes, have been reported in some animal studies with dogs, rabbits and swine (Rubin and Barnett, 1967; Smith et al. 1969)[3] and in guinea pigs (Rengstarff et al., 1972)[4], it was subsequently demonstrated that the ocular effect was species-specific and was not reproducible in primates, including humans (Smith et al., 1969)[3] (de la Torre et al. 1981)[5]. Furthermore, full ophthalmologic examinations revealed no DMSO-related lenticular changes in any of 84 patients treated three times daily for three months with topical 70% DMSO, topical 2% DMSO or 0.85% normal saline (maximum theoretical dosage of 2.6 g DMSO/kg/day), which is comparable to dosages used in the animal studies (Shirley et al., 1988)[6].

Human and Animal Metabolism

DMSO is metabolized in humans by oxidation to dimethyl sulfone, $DMSO_2$ or by reduction to dimethyl sulfide, DMS. DMSO and $DMSO_2$ are excreted in the urine and feces. DMS is eliminated through the breath and skin with a characteristic "garlic" or "oyster-like" odor. Human excretion of orally administered DMSO is complete within 120 hours, with urinary excretion being the primary pathway. The rate of renal clearance has been shown to be similar for chronic and singly administered doses regardless of dose concentration. No residual accumulation of DMSO has been reported in humans or lower animals who have received DMSO treatment for protracted periods of time, regardless of route of dose administration.

Metabolite Toxicity

The metabolites of DMSO are $DMSO_2$, which naturally occurs at low levels in human urine (PDR, 1994)[8], and DMS, which naturally occurs in plants, the atmosphere, and lakes and oceans (Pearson et al., 1981)[9]. Both of these metabolites are readily excreted from the body. Based on their widespread natural occurrence and ready degradation and/or excretion, the production of these metabolites from the proposed use of DMSO on food producing plants is not expected to pose any toxicological concern.

Inhalation

Fishman and coworkers at the Naval Medical Center [10] performed many toxicological measurements on the exposure of rats to DMSO vapors. The following single and repeated exposures were made:

DMSO Concentration	**Length of Exposure**
1600 milligrams per cubic meter	4 hours
2900 milligrams per cubic meter	24 hours
2000 milligrams per cubic meter	40 hours
200 milligrams per cubic meter	210 hours (7 hrs/day, 5 days/week for 30 exposures

Extensive blood and tissue samples were examined. No outward toxic signs were shown. No significant changes were noted during or following repeated exposure. We suggest, as a good hygiene practice, avoiding exposure to DMSO sprays or mists and very high doses of DMSO vapors.

Effects on Other Organisms

1. Effects on Plants. DMSO by itself and DMSO with antibiotics, minerals, nutrients, pesticides and other materials have been sprayed on, injected into, painted on, and fed to a variety of plants. It has a low order of phyto-toxicity in these applications.

2. Effects on Fish. Wilford[11] investigated the toxicity of DMSO in water to 9 species of fish. At 96 hours, the LC-50 was 32,000 to 43,000 ppm DMSO (3-4%). This is far less toxic than acetone (fingernail polish remover) and other widely used solvents.

3. Effects on Sewage Plants.
DMSO is biodegradable in biological systems, it is converted in part to methyl sulfone and to dimethyl sulfide. The sulfone is stable and inert and degraded only slowly by microorganisms or physical factors. At high concentrations, some DMS may escape, producing its characteristic odor.

Natural Occurrences in Food.
The occurrence of DMSO and its metabolites, dimethyl sulfide and methyl sulfone ($DMSO_2$), have been widely reported in a variety of foods. Pearson [9] and coworkers reported finding 0.07 to 16 ppm DMSO, along with $DMSO_2$, in 14 fruits, vegetables or beverages. This natural occurrence insures that the body can dispose of DMSO by well-established metabolic processes. Naturally-occurring DMSO has been identified in alfalfa, asparagus, barley, beans, beets, cabbage, corn, cucumbers, oats, onions, Swiss chard, tomatoes, apples, raspberries, spearmint, beer, milk, coffee and tea. DMSO concentrations in fresh fruits, vegetables and grains ranged from undetectable (<0.05 parts per million) to 1.8 ppm.

Genotoxicity

DMSO is not mutagenic to *Salmonella, Drosophila*, and fish cell cultures. Because DMSO is so non-reactive as a mutagen, it is widely used as a solvent in mutagenicity testing. Although DMSO is bacteriostatic or bactericidal at concentrations of 5-50%, there is no evidence that DMSO causes chromosomal aberrations at levels that are not directly toxic to cells. Bone marrow smears from primates (rhesus monkeys) that received oral or topical doses of DMSO for 18 months showed no DMSO effects (Vogin et al., 1970)[12]. An *in vivo* cytogenetics study of DMSO administered by intraperitoneal injection to male rats found a significant increase in aberrant femoral bone marrow cells when compared to controls (Kapp and Eventoff, 1980)[13]. However, evidence from the *Salmonella* studies and other toxicology data, especially the teratology data, suggests that the increase in aberrant femoral cells likely resulted from direct toxicity of DMSO injected into an animal instead of a classic "mutagenic" response.

According to Brayton (1986), there are no documented adverse genetic effects reported as a result of medicinal DMSO uses (including quasi-medicinal uses for treatment of arthritis or sprains and strains). Additionally, no adverse genetic effects have been reported from occupational exposure to DMSO in over 40 years of industrial

use (Brayton, 1986). There is no evidence that DMSO causes chromosomal aberrations at levels that are not directly toxic to cells.

Reproductive and Developmental Toxicity

A mouse teratology NOEL of 12 g/kg/day has been established based on research with a 50% DMSO solution administered orally. Additional teratogenicity studies of orally administered DMSO to pregnant mice, rats, rabbits and guinea pigs have demonstrated that DMSO is not a teratogen in mammals except at high levels that cause overt maternal toxicity and are coincident with the maximum tolerated dose. The data suggest that DMSO is not teratogenic at low levels regardless of the route of administration. Finally, the teratogenic potential of DMSO is dependent on the route of administration, the dose level and gestation stage at exposure.

The one study (Robens, 1968) that did show evidence of teratogenic effects (in hamsters, one of three animal species tested) from oral administration of DMSO is inappropriate to use for a teratologic evaluation of DMSO for the following reasons:

- DMSO was not the compound of interest but was used only as a solvent control at two very high dose levels which precluded establishing a NOEL.

- One of the DMSO levels tested resulted in maternal death and was clearly beyond the maximum tolerated dose (MTD).

DMSO is not considered to be directly embryotoxic and has been shown to be a successful cryoprotectant for mammalian semen and embryos (Brayton, 1986).

In summary, the evidence of the above teratology data suggests that:

1. DMSO is not a teratogen to mammals when administered via oral and dermal routes at dose levels that do not produce overt maternal toxicity.
2. DMSO is not a teratogen at low dose levels regardless of the route of administration.
3. The teratogenic potential of DMSO is dependent on route of administration, the dose level and the gestational time of exposure.

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